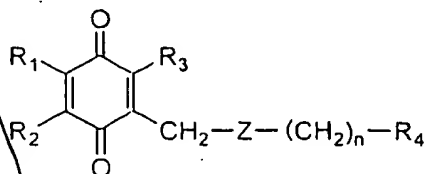


CLAIMS

composition

1. An NF-kB inhibitor comprising as an active ingredient a benzoquinone derivative represented by the following general formula (1):



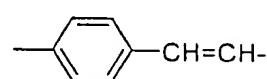
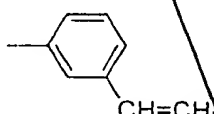
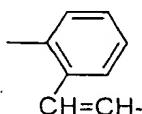
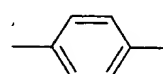
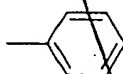
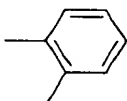
(1)

wherein

R₁, R₂, and R₃ are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

R₄ is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;

Z is



and, n is an integer from 0 to 6, or its hydroquinone form, or a pharmaceutically acceptable salt thereof.

composition

2. The NF-kB inhibitor according to claim 1 ~~in~~ ^{wherein} R₁ and R₂ are a hydrogen atom, a methyl group, or a methoxy group.

composition

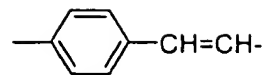
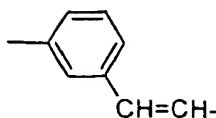
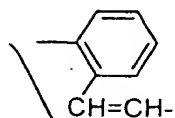
3. The NF-kB inhibitor according to claim 1 ~~or 2~~ ^{wherein} R₃ is a hydrogen atom or a methyl group.

composition

4. The NF-kB inhibitor according to claim 1, 2, or 3 ^{wherein} Z is

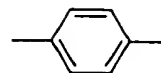
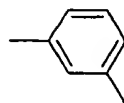
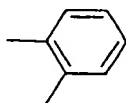
[^]

a B 30
a
a B
a B 35
a



and n is an integer 0.

5. The NF- κ B inhibitor according to claim 1, 2, or 3 wherein Z is



and n is an integer 1, 2, or 3.

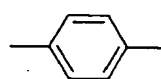
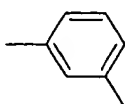
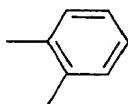
6. The NF- κ B inhibitor according to ~~any one of~~ claims 1 to 5 wherein R_4 is a group $-COOR_5$, wherein R_5 is a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted phenyl group, or an optionally substituted aralkyl group having 7 to 11 carbons.

7. The NF- κ B inhibitor according to ~~any one of~~ claims 1 to 5 wherein R_4 is a group $-CONR_6R_7$, wherein R_6 and R_7 are each independently a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted bicyclic unsaturated or partially saturated hydrocarbon ring group having 9 to 11 carbons, an optionally substituted heterocyclic group, an optionally substituted phenyl group, an optionally substituted aralkyl group having 7 to 11 carbons, or a heteroaryl- C_1 - C_3 -alkyl group, or R_6 and R_7 , together with the nitrogen atom to which they are attached, represent a heterocyclic group which may further contain a nitrogen, oxygen, and/or sulfur atom.

8. The NF- κ B inhibitor according to ~~any one of~~ claims 1 to 5 wherein R_4 is a group $-CONR_6R_7$, wherein R_6 and R_7 , together with the nitrogen atom to which they are attached, represent a 5- to 10-membered optionally

substituted, nitrogen-containing heterocyclic group which may contain, in addition to the carbon and nitrogen atom, 1 to 3 heteroatoms selected from the group consisting of a nitrogen, oxygen and sulfur atom, the carbon atom on said cyclic group being optionally a ketone form or the sulfur atom on said cyclic group being optionally an oxide form.

9. The NF- κ B inhibitor according to claim 1, ~~6, 7, 8~~ ^{wherein} ~~in which~~ ^{wherein} R_1 and R_2 are a methyl group or a methoxy group; R_3 is a methyl group; R_4 is a carboxyl group which is optionally esterified or amidated; Z is



and n is an integer 1, 2, or 3.

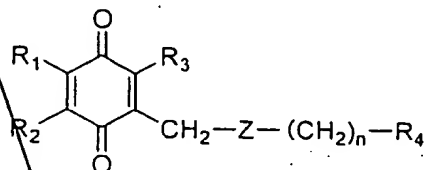
10. The NF- κ B inhibitor according to ~~any one of~~ ^{wherein the} ~~claims 1 to 9~~ ^{is} which is a suppressing agent for the gene expression of one or more substances selected from the group consisting of IL-1, TNF- α , IL-2, IL-6, IL-8, iNOS, granulocyte colony-stimulating factor, interferon- β , ICAM-1, VCAM-1, ELAM-1, major histocompatibility system class I, major histocompatibility system class II, β 2-microglobulin, immunoglobulin light chain, serum amyloid A, angiotensinogen, complement B, complement C4, c-myc, HIV, HTLV-1, SV40, CMV, and adenovirus.

11. The NF- κ B inhibitor according to ~~any one of~~ ^{wherein the} ~~claims 1 to 9~~ which is a preventive or therapeutic agent for inflammatory diseases.

12. The NF- κ B inhibitor according to ~~any one of~~ ^{wherein the} ~~claims 1 to 9~~ which is a preventive or therapeutic agent for autoimmune diseases.

13. The NF- κ B inhibitor according to ~~any one of~~ ^{wherein the} ~~claims 1 to 9~~ which is a preventive or therapeutic agent for viral diseases.

14. A preventive or therapeutic agent for diseases caused by the activation of NF- κ B comprising as an active ingredient a benzoquinone derivative represented by the following general formula (1):



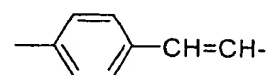
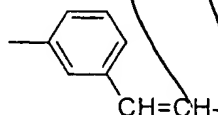
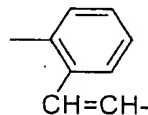
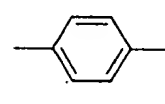
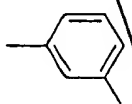
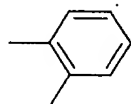
(I)

wherein

R_1 , R_2 , and R_3 are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

R_4 is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;

Z is



and, n is an integer from 0 to 6, or its hydroquinone form, or a pharmaceutically acceptable salt thereof.

15. A novel compound selected from:

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]morpholine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]thiomorpholine S-oxide,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-

push
C3

C³
cont⁵

10

15

20

25

30

35

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]thiomorpholine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]dimethylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]isopropylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]ethanolamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]benzylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]phenethylamine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]thiomorpholine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]morpholine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-

C3
cont

5

10

✓

20

30

1. The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a continuous function and that it satisfies the functional equation $f(x+y) = f(x) + f(y)$. The function $f(x)$ is also shown to be differentiable and its derivative is found to be $f'(x) = f(x)$.

C³
cont⁵

10

15

20

25

30

35

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-(s)-(-)-1-phenylethylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-

benzoquinon-2-ylmethyl)phenyl]propionyl]-(R)-(+)-1-phenylethylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-1,3-dimethylbutylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]cycloheptylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-3,5-dimethylpiperidine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-ethoxycarbonylpiperazine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-phenylpiperazine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-hydroxy-4-phenylpiperidine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-(4-chlorophenyl)-4-hydroxypiperidine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-(2-methoxyphenyl)piperazine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline,

4-acetyl-4-phenyl-1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-1,2,3,4-tetrahydroisoquinoline,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isoamylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-

C3
cont 5

benzoquinon-2-ylmethyl)phenyl]propionyl]cyclohexylamine,
N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-
benzoquinon-2-ylmethyl)phenyl]propionyl]-4-
hydroxyaniline,
4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)benzoic acid,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)benzoyl]morpholine,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)benzoyl]isopropylamine,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)benzoyl]piperidine,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)benzoyl]thiomorpholine,
3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)benzoic acid,
N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)benzoyl]isopropylamine,
N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)piperidine,
N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)morpholine,
N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)thiomorpholine,
4-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)phenyl]-n-butyric acid,
N-[4-[4-(5,6-dimethoxy-3-methyl-1,4-
benzoquinon-2-ylmethyl)phenyl]butanoyl]morpholine,
N-[4-[4-(5,6-dimethoxy-3-methyl-1,4-
benzoquinon-2-ylmethyl)phenyl]butanoyl]thiomorpholine,
N-[4-[4-(5,6-dimethoxy-3-methyl-1,4-
benzoquinon-2-ylmethyl)phenyl]butanoyl]piperidine,
N-[4-[4-(5,6-dimethoxy-3-methyl-1,4-
benzoquinon-2-ylmethyl)phenyl]butanoyl]isopropylamine,
4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-
ylmethyl)phenylacetic acid,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-

5

10

15

20

25

30

35

C3
cont

ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED
DATE 08-11-2010 BY 60322 UCBAW

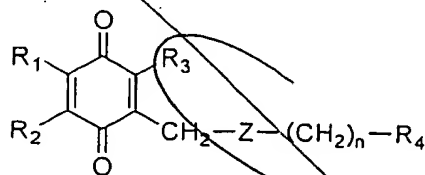
C3
cont

ylmethyl)phenylacetyl]morpholine,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]piperidine,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]thiomorpholine,
N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]isopropylamine,
3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetic acid,
10 N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]piperidine,
N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]thiomorpholine,
N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]morpholine,
15 N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]morpholine,
4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]-n-butyric acid,
20 N-[4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]piperidine,
N-[4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]thiomorpholine,
N-[4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]morpholine, and
25 N-[4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]isopropylamine.

B

16. An ~~inhibitor of~~ ^{inhibitor composition} TNF- α production comprising as an active ingredient a benzoquinone derivative represented by the following general formula (1):

35



(I)

wherein

5 ~~R₄ is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;~~

10

~~inhibitor~~ inhibitor composition

inhibitor composition

wherein
or 17 i

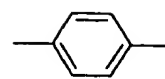
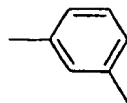
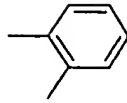
inhibitor composition
of TNF α production according

 $\text{CH}=\text{CH}-$

inhibitor composition

wherein

13
a



and n is an integer 1, 2, or 3.

21. The ~~inhibitor of~~ ^{inhibitor composition} TNF- α production according to ~~any one of claims 16 to 20~~ ^{wherein} in which R_4 is a group $-COOR_5$, wherein R_5 is a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted phenyl group, or an optionally substituted aralkyl group having 7 to 11 carbons.

22. The ~~inhibitor of~~ ^{inhibitor composition} TNF- α production according to ~~any one of claims 16 to 20~~ ^{wherein} in which R_4 is a group $-CONR_6R_7$, wherein R_6 and R_7 are each independently a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted bicyclic unsaturated or partially saturated hydrocarbon ring group having 9 to 11 carbons, an optionally substituted heterocyclic group, an optionally substituted phenyl group, an optionally substituted aralkyl group having 7 to 11 carbons, or a heteroaryl- C_1 - C_3 -alkyl group, or R_6 and R_7 , together with the nitrogen atom to which they are attached, represent a heterocyclic group which may further contain a nitrogen, oxygen, and/or sulfur atom.

23. The ~~inhibitor of~~ ^{inhibitor composition} TNF- α production according to ~~any one of claims 16 to 20~~ ^{wherein} in which R_4 is a group $-CONR_6R_7$, wherein R_6 and R_7 , together with the nitrogen atom to which they are attached, represent a 5- to 10-membered optionally substituted, nitrogen-containing heterocyclic group which may contain, in addition to the carbon and nitrogen atom, 1 to 3 heteroatoms selected from the group consisting of a nitrogen, oxygen and sulfur atom, the carbon atom on said cyclic group being optionally a ketone form or the sulfur atom on said cyclic group being optionally an oxide form.

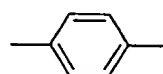
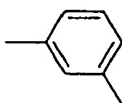
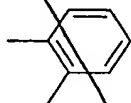
24. The ~~inhibitor of~~ ^{inhibitor composition} TNF- α production according to

a

wherein

Claim 16, ~~21, 22, or 23 in which~~ ^{wherein} R₁ and R₂ are a methyl group or a methoxy group; R₃ is a methyl group; R₄ is a carboxyl group which is optionally esterified or amidated; Z is

C4
cont



and n is an integer 1, 2, or 3.

B

10

25. The ~~inhibitor of~~ ^{inhibitor composition} TNF- α production according to

a

a

~~any one of claims 16 to 24 which is~~ ^{wherein the} a suppressing agent for the gene expression of one or more substances ^{is} selected from the group consisting of IL-1, TNF- α , IL-2, IL-6, IL-8, iNOS, granulocyte colony-stimulating factor, interferon- β , ICAM-1, VCAM-1, ELAM-1, plasminogen activator-inhibiting factor I, major histocompatibility system class I, major histocompatibility system class II, β 2-microglobulin, immunoglobulin light chain, serum amyloid A, angiotensinogen, complement B, complement C4, c-myc, HIV, HTLV-1, SV40, CMV, and adenovirus.

20

^{inhibitor composition}

26. The ~~inhibitor of~~ TNF- α production according to

~~any one of claims 16 to 24 which is~~ a preventive or therapeutic agent for inflammatory diseases.

^{inhibitor composition}

27. The ~~inhibitor of~~ TNF- α production according to

~~any one of claims 16 to 24 which is~~ a preventive or therapeutic agent for autoimmune diseases.

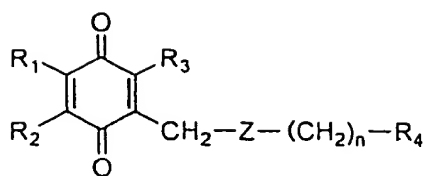
^{inhibitor composition}

28. The ~~inhibitor of~~ TNF- α production according to

~~any one of claims 16 to 24 which is~~ a preventive or therapeutic agent for viral diseases.

30

29. A preventive or therapeutic agent for diseases caused by the excessive production of TNF- α comprising as an active ingredient a benzoquinone derivative represented by the following general formula (1):



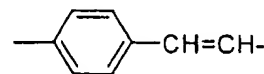
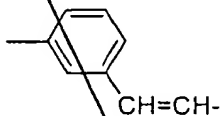
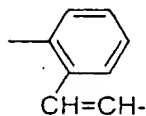
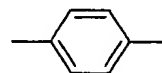
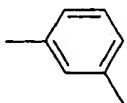
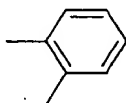
(I)

wherein

R_1 , R_2 , and R_3 are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

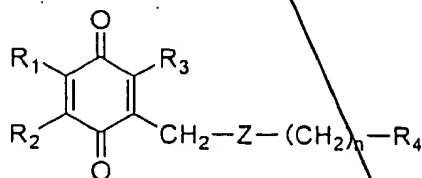
R_4 is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;

Z is



and, n is an integer from 0 to 6, or its hydroquinone form, or a pharmaceutically acceptable salt thereof.

30. A benzoquinone derivative represented by the following general formula (1):



(I)

wherein

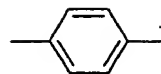
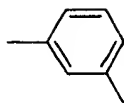
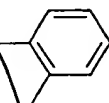
R_1 , R_2 , and R_3 are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

R_4 is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally

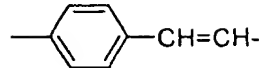
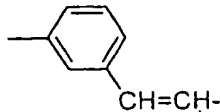
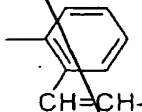
esterified or amidated;

Z is

5

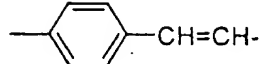
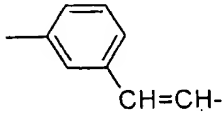
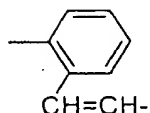


10



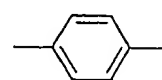
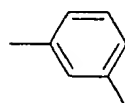
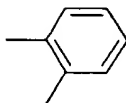
and, n is an integer from 0 to 6,
provided that when Z is

15



n is not 0, and when Z is

20



n is neither 0 nor 2,
or its hydroquinone form, or a pharmaceutically
acceptable salt thereof.

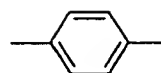
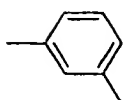
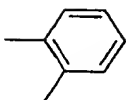
25

31. The benzoquinone derivative according to claim
30 wherein R_1 and R_2 are a hydrogen atom, a methyl
group, or a methoxy group, or its hydroquinone form or a
pharmaceutically acceptable salt thereof.

30

32. The benzoquinone derivative according to claim
30 wherein R_3 is a hydrogen atom or a methyl
group, or its hydroquinone form or a pharmaceutically
acceptable salt thereof.

33. The benzoquinone derivative according to claim
30 wherein Z is



5 and n is an integer 1 or 3, or its hydroquinone form or a pharmaceutically acceptable salt thereof.

a 34. The benzoquinone derivative according to ~~any one of claims 30 to 33~~ ^{wherein} in which R_4 is a group $-COOR_5$, wherein R_5 is a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted phenyl group, or an optionally substituted aralkyl group having 7 to 11 carbons, or its hydroquinone form or a pharmaceutically acceptable salt thereof.

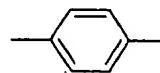
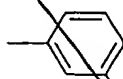
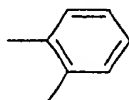
a 35. The benzoquinone derivative according to ~~any one of claims 30 to 33~~ ^{wherein} in which R_4 is a group $-CONR_6R_7$, wherein R_6 and R_7 are each independently a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted bicyclic unsaturated or partially saturated hydrocarbon ring group having 9 to 11 carbons, an optionally substituted heterocyclic group, an optionally substituted phenyl group, an optionally substituted aralkyl group having 7 to 11 carbons, or a heteroaryl- C_1 - C_3 -alkyl group, or R_6 and R_7 , together with the nitrogen atom to which they are attached, represent a heterocyclic group which may further contain a nitrogen, oxygen and/or sulfur atom, or its hydroquinone form or a pharmaceutically acceptable salt thereof.

a 36. The benzoquinone derivative according to ~~any one of claims 30 to 33~~ ^{wherein} in which R_4 is a group $-CONR_6R_7$, wherein R_6 and R_7 , together with the nitrogen atom to which they are attached, represent a 5- to 10-membered optionally substituted, nitrogen-containing heterocyclic group which may contain, in addition to the carbon and nitrogen atom, 1 to 3 heteroatoms selected from the group consisting of a nitrogen, oxygen and sulfur atom, the carbon atom on said cyclic group being optionally a ketone form or the sulfur atom on said cyclic group being

optionally an oxide form, or its hydroquinone form or a pharmaceutically acceptable salt thereof.

37. The benzoquinone derivative according to claim 30, ^{wherein} ~~34, 35, or 36~~ in which R₁ and R₂ are a methyl group or a methoxy group; R₃ is a methyl group; R₄ is a carboxyl group which is optionally esterified or amidated; Z is

10



and n is an integer 1 or 3, or its hydroquinone form or a pharmaceutically acceptable salt thereof.

add
D5

add
G1